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According to present-day notions, the decisive role in the development of hypertension is played by traumatization and emotional strain in the sphere of the upper nervous activity, resulting in the rise of congested foci of stimulation in the upper vasomotor centers (G. F. Lang). Experimental reproduction of hypertension through disturbance of the blood supply to the kidneys (Goldblat, Page, L. N. Karlik, I. I. Burachevskiy) has served as a beginning for the study of the role of renal ischemia in the pathogenesis of hypertension.

Goldring, Ranges, Chasis and Smith, N. I. Ivanov, N. A. Ratner, N. L. Kikodze, P. M. Kireyev and others have revealed the rise of renal ischemia from the first periods of hypertension. In their research, the diminution of renal blood flow in the first stage of hypertension resulted in an increase in filtration; in the later periods of the disease there was a pronounced diminution of the renal blood flow and filtration. According to the data obtained, the authors affirm that ischemia of the kidneys in hypertension arises early as a result of the general narrowing of the abducent glomerate arterioles, which increases the filtration pressure in the glomerules and decreases the blood supply to the postglomerular segments of the ducts. However, the rise of ischemia of the kidneys and its progression in hypertension have not been observed in all cases.

Castleman and Smithwick, M. Ya. Ratner, P. I. Mishchenko, N. L. Kikodze, G. F. Blagman, E. I. Estrin and Ye. I. Zaytseva have established the presence of normal renal blood flow in most of the patients in stage I and in the smaller part of patients in stage II of hypertension.

Considering the contradictoriness of the data on the time of the rise of ischemia of the kidneys in hyper-

tension, we have made an investigation of this question, using clinical data in comparison with the condition of general and renal hemodynamics. Under observation were 256 patients; the state of the blood supply to the kidneys was determined in 80 of them.

Proceding from the fact that ischemia of the kidneys from the initial stages of hypertension should lead to the early appearance of pathological elements in the urine, we investigated 256 patients in stages I, II and III of hypertension for the purpose of ascertaining the frequency and duration of the changes in the urine. Table 1 illustrates the dependence between high arterial pressure and pathological changes in the urine.

Table 1

Relationship Between Changes in the Urine and the Level of Arterial Pressure

Result of Examination of Blood	Arterial Pressure in mm					
	140/80	150/90	160/95	170/100	180/110	190/120 – 220/150
	Number of Patients					
Changes lacking	16	99	56	22	13	15
Persistent albuminuria and hematuria	--	--	1	2	3	14
Traces of albumin and isolated erythrocytes	5	9	4	5	2	--

From table 1 it may be seen that changes in the urine were absent in the overwhelming majority of patients (211, or 82.5%). Various degrees of albuminuria and hematuria were discovered in 45 patients (17.5%). In only 20 patients were the pathologic changes in the urine persistent; in the remaining 25, traces of albumin and isolated erythrocytes were discovered in the initial examination, but were absent in succeeding analyses. Pathologic changes in the urine were determined both with a small rise in arterial pressure and with a considerable increase in it. The difference was that, with a small or moderate irse in arterial pressure, the changes in the urine were insignificant and of short duration, whereas with very high arterial pressure the albuminuria and hematuria were more pronounced and lasted for a long time. The frequency of cases with persistent pathological changes in the urine increased as the arterial pressure

grew. However, it is a striking fact that no changes in the urine were discovered in half the patients with an arterial pressure of 190/120-220/150 mm.

It may be supposed that the absence of changes in the urine in such patients is to be explained by the development of compensatory-adaptive reactions in the vascular channel of the kidneys in response to a rise in the general arterial pressure. The appearance of traces of albumin and isolated erythrocytes in the urine with a small rise in arterial pressure was evidently due to the non-adaptability of the vascular channel of the kidneys to the fluctuations of the arterial pressure.

To ascertain the causes of the pathologic changes in the urine, we studied the condition of general and renal hemodynamics in hypertension cases. The per-minute volume of blood circulation, the arterial pressure and the rate of spread of the pulse wave through the vessels of an elastic type were studied by the mechano-cardiographic technique of N. N. Savitskiy with the use of the Bremser-Ranke physical method.

Thetechnique of determining renal blood flow. In the morning, under conditions of basic metabolism, the subject is given 1.5 liters of water to drink; $1\frac{1}{2}$ hours after this begins examination of renal blood flow. To create initial concentration of perabrodil in the blood within limits of 1-1.5 mg%, 2.5 ml of a 35% solution of perabrodil is administered intravenously, after which the concentration thus created is maintained for 60-70 minutes by an intravenous drop injection of 2-2.5 ml of the same solution, diluted in 20 ml of the physiological solution. From the moment of injection of the maintaining solution, a record is kept of the arterial pressure and pulse from the carotid and the abdominal aorta at the place where the latter divides into the hypogastric arteries. Then the patient voids the bladder. Next, separate portions of urine are collected every 20 minutes. In the middle of the 20-minute interval 15 ml of blood are taken from a vein and placed in a centrifuge tube with sodium oxalate.

The iodine concentration in the blood plasma and urine was determined by the Bak, Braun and Raaschou technique. (For a detailed description see N. I. Ivanov's articles).

After centrifuging the blood, the plasma is carefully removed with a pipette and transferred to a second test tube; then 3 ml of plasma are measured out and again transferred to a small glass. To 3 ml of blood

plasma are added 21 ml of distilled water for dilution, 3 ml of 0.64 N solution of sulfuric acid and 3 ml of a 10% solution of sodium tungstate to precipitate the albumin. After precipating the albumins, the solution is filtered through a folded paper filter. From each portion of albuminless filtrate are taken 3 samples of 4 ml each and these are placed in separate small flasks with wide necks. To the second sample is added 0.15 ml of a four-mol solution of sulfuric acid and 0.3 ml of a 7% solution of potassium hypermanganate. All nine samples of albuminless filtrate of blood plasma and three control samples are placed in a boiling water bath for 10-15 minutes. Then the samples are taken out and a 7% solution of sodium nitrite is added to them in drops, being carefully shaken, until the solutions are completely decolorized. To the decolorized samples is added 1 ml of a 30% solution of urea to remove the excess sodium nitrite. The sample is again shaken and placed in a boiling water bath; it is shaken a second time until the carbon dioxide bubbles are completely removed and then taken out and cooled in ice water. To the cooled samples is added 0.1 ml of a freshly prepared solution of potassium iodide in the proportion of 2 ml to 3 ml of water. After they have stood for 10 minutes in a dark, cool place, 0.1 ml of a 0.5% solution of starch is added to the samples and then they are titrated with a 1/400 N solution of sodium thiosulfate.

Under the influence of the potassium permanganate and sulfuric acid, the iodine in the molecule of perabrodil is oxidized with formation of potassium iodate. In the presence of potassium iodide and sulfuric acid, the potassium iodate forms 6 molecules of iodine. The reaction proceeds according to the following formula:

$$2KIO_3 + 10KI + 6H_2SO_4 = 6I_2 - 6K_2SO_4 + 6H_2O.$$

The iodine content in the blood plasm is calculated by the following formula:

$$Q = \frac{0.053 \cdot 10 \cdot 100 \cdot T,}{4}$$

where Q is the iodine concentration in mg%, 10 the dilution of the blood plasma, 100 the recomputation per 100 ml of blood plasma, T the amount of thiosulfate used in titration. The atomic weight of iodine is 126.92. The oxidizing gram-equivalent of ;iodine is $\frac{126.92}{6} = 21.15.$

hence, 1 ml of a one-mol solution of thiosulfate corre-

sponds to 21.15 mg of iodine, and 1 ml of a 1/400 N solution of it corresponds to 0.053 mg of iodine.

The iodine concentration in the urine was determined by exactly the same technique, except for the manipulations in the precipitation of the albumins.

The coefficient of purification of perabrodil (plasma flow) and the renal blood flow were computed by the following formulas: $Pl = \frac{Iu.\ Md.}{I_b}$; $K_b = \frac{Pl.100.}{G}$

where Pl is the coefficient of purification of perabrodil, or plasma flow, Iu the iodine concentration in the urine, I_b the iodine concentration in the blood, Md the per-minute diuresis, K_b the kidney blood flow, and G the percentage of plasma in the blood.

Seventeen practically healthy persons and 80 hypertension patients were examined by the above described technique.

In the control group the kidney blood flow was 900-1300 ml per minute, the per-minute volume of circulation 3900-5200 ml. With respect to the general hemodynamics, the kidney blood flow was 21-27% of the per-minute volume of circulation. The same dependence of the kidney blood supply upon the general hemodynamics was established by Bolomey and Bredly; according to these authors, the kidney blood flow is 20-30% of the per-minute volume. From this it follows that the per-minute volume of the circulation exerts a definite influence upon the magnitude of the kidney blood flow.

The condition of the blood supply to the kidneys in stage I of hypertension was studied in 40 males aged 20-45. The arterial pressure in the patients examined was within limits of 150/90 and 190/120 mm; the function of the kidneys was good, changes in the urine were absent. In this group of patients, the kidney blood flow was 947-1800 ml per minute, the per-minute volume of circulation 4000-7000 ml (table 2).

The different magnitudes of the kidney blood flow were determined by the passability of the precapillary channel and by the magnitude of the per-minute volume of the circulation. The figure shows the dependence of the kidney blood flow upon the per-minute volume of circulation.

Table 2

Kidney Blood Flow in Various Stages of Hypertension

Group of Patients Examined	Kidney Blood Flow in ml											
	150	400	500	600	700	800	900	1000	1100	1200	1300	1400-1800
Control Group	—	—	—	—	—	—	2	6	4	3	2	—
Patients in Stage I	—	—	—	—	—	—	1	7	3	6	10	13
Stage II	—	1	2	4	3	3	3	3	3	4	4	4
Stage III	2	1	—	1	2	—	—	—	—	—	—	

Dependence of Effective Kidney Blood Flow Upon Per-Minute Volume of Circulation

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Legend: A) Effective kidney flow in ml; B) Per-minute volume in ml; C) Stage I of hypertension; D) Stage II of hypertension

In Stage I of hypertension theratio between the kidney blood flow and the per-minute volume was determined in 21 patients out of 40. In 16 of them the kidney blood flow was 21-27% of the per-minute volume, which is reflected in the figure by the approach of the little circles to the line of proportionality; in three patients this ratio was found to be increased (28-32%) and in two diminished (20-19%).

The above data show that the ratio of the kidney blood flow to the per-minute volume in most patients in hypertension stage I remains normal; only in a small number of them is it disturbed in the direction of an increase or decrease.

The magnitude of the kidney blood flow is affected by the passability of the precapillary channel. The total resistance of the precapillary channel of the kidneys is computed by the Poisel (?) formula transformed by N. B. Savitskiy:

$$W = \frac{P \cdot T}{Q} \cdot 1333,$$

where W is the total resistance of the precapillary channel of th kidneys, P the average pressure, T the time in seconds, Q the kidney blood flow in ml per minute, 1333 the factor for conversion of the pressure, expressed in millimeters of mercury, into dynes.

Normally, the total resistance of the precapillary channel of the kidneys was 5500-6500 dynes times cm^{-1} times $seconds^{-5}$. In hypertension stage I the passability of the precapillary channel proved to be normal in 7 patients and increased from 7000 to 9000 dynes times cm^{-1} times $seconds^{-5}$ in the remaining 14 patients (Table 3).

Table 3

Resistance of the Precapillary Channel in Various Stages of Hypertension

Group of Patients	Resistance of the Precapillary Channel (in Dynes $\cdot$ cm^{-1} $\cdot$ sec^{-5})								
	5500	6000	6500	7000	8000	9000	11000-15000	20000	85000
Control Group	3	4	10	—	—	—	—	—	—
Patients in Stage I	4	2	1	3	8	3	—	—	—
In Stage II	—	—	—	—	1	2	7	2	—
In Stage III	—	—	—	—	—	—	1	4	1

The blood supply to the kidneys in hypertension stage II was studied in 34 males aged 22-66. The arterial pressure in this group kept persistently at a high level; the minimum pressure was 100-140 mm, the maximum 160-220 mm. Hypertonic retinopathia was determined in all the patients; albuminuria and hematuria with a lowering of the concentrating power of the kidneys was detected in 13. The kidney blood glow andits ratio to the per-minute volume were found to be the same as in stage I in all the patients in which pathologic changes in the urine were absent. Diminution of the kidney blood flow was detected in 13 patients with pathologic changes in the urine, the kidney blood flow in such cases being 11-16% of the per-minute volume (see table 2 and figure). The degree of diminution of the kidney blood flow depended upon the extent of the changes in the urine, especially upon the lowering of the concentrating capacity of the kidneys. The diminution of that part of the per-minute volume which determines the blood supply to the kidneys indicated a pronounced difficulty in the movement of the blood through the vessels of the kidneys.

This is attested by the presence of the sharply

increased resistance of the precapillary channel of the kidneys (11,000-20,000 dynes $\cdot$ cm^{-1} $\cdot$ sec $^{-5}$).

Stage III of hypertension was found in 6 patients aged 22-45. In this group more pronounced changes in the back of the eye and in the urine were noted; the arterial pressure kept persistently at a very high level: minimum 130-150 mm, maximum 230 mm. The kidney blood flow in 4 patients was 400-700 ml; in two with nitrogenemia (azotemiya) it was 150-200 ml. This diminution of the blood supply to the kidneys was caused by the sharply increased resistence of their vascular channel, since the resistance to the blood flow reached 20,000-85,000 dynes $\cdot$ cm^{-1} $\cdot$sec^{-5}.

The sharp decrease in the kidney blood flow and the increase in the resistance of the precapillary channel of the kidneys indicate the development of arteriolosclerotic changes with a wasting and sclerosis of a large part of the neurons. Ischemia of the kidneys results in organic changes in them, the appearance of albumin and erythorcytes in the urine and a reduction in the concentrating capacity of the kidneys. It is impossible to imagine the rise of ischemia in the kidneys without organic changes in them and without the appearance of pathologic elements in the urine. In stage I of hypertension ischemia of the kidneys is absent; hence, no pathological changes in the urine are detected. They appear in stage II, when a diminution of the blood supply to the kidneys takes place. In the initial periods, ischemia of the kidneys is inconstant, since it disappears under the influence of sedatives and vessel-expanding drugs, which indicates the rise of spastic phenomena in the vessels of the kidneys. In subsequent periods, when the concentrating capacity of the kidneys is being lowered, ischemia of the kidneys becomes persistent. Proof of this are the data on repeated examinations of the kidney blood flow of eight patients after use of the sleep-inducing drugs diabasol and papaverine.

From table 4 it may be seen that in 5 patients with slight albuminuria and hematuria but without disturbance of the concentrating capacity of the kidneys the kidney blood flow was increased all the way to normal; in three patients with lowered concentrating capacity of the kidneys there was no restoration of the blood flow. The total resistance of the kidney arterioles dropped distinctly after treatment. Consequently, the increase in the blood flow was due to a decrease in the spastic pehnomena in the vascular channel of the kidneys.

Table 4

Change in the Function of the Kidneys of Hypertension Patients in Dynamics

(after treatment with antispastic drugs)

Serial No	date of examination	Arterial pressure in mm Minimum	mean	Maximum	Kidney blood flow in ml per minute	Resistance of kidney vessels in dynes$\cdot$cm^{-1}$\cdot$sec^{-5}	Specific weight of urine
1	14/IV 13/V	120 130	145 142	205 200	755 1200	15240 9464	1010-1021 1010-1025
2	27/V 25/VI	120 108	138 125	200 170	550 1100	20069 9088	1002-1021 1006-10[illegible]
3	20/V 27/VI	120 115	137 135	225 220	550 980	19922 10995	1010-1022 1016-1031
4	25/II 25/III	95 95	120 120	170 170	576 1300	16662 7382	1012-1023 1016-1024
5	30/IV 20/V	100 105	125 125	170 170	800 1200	15829 10553	1010-1024 1015-1026
6	20/III 20/IV	120 125	140 140	220 220	650 800	17226 14000	1010-1015 1015-1021
7	24/X 26/XII	140 130	160 160	230 215	660 600	19400 21328	1002-1015 1008-1018
8	24/IV 28/V	130 125	160 155	220 215	170 200	75275 63884	1004-1008 1004-1008

Despite the increase in passability of the pre-capillary channel of the kidneys and the improvement in the blood supply to them, the arterial pressure was not lowered substantially, which indicated the absence

of a direct dependence of the arterial pressure upon renal ischemia. This is attested by the data on the comparison of the magnitudes of the arterial pressure and the volume of the kidney blood flow in the patients examined. From table 5 it may be seen that normal or even an increased kidney blood flow was detected not only when the arterial pressure was raised just a little, but also when its level was very high. One is struck by the circumstance that a diminution of the blood flow of the kidneys may occur both at moderate and at very high arterial pressure. This may serve as an indirect proof that spastic phenomena in the kidney vessels play a decisive role in the diminution of the blood supply to the kidneys.

Table 5

Comparison of the Level of Arterial Pressure and the Magnitude of Kidney Blood Flow

Kidney Blood Flow in ml per Minute	Arterial Pressure in mm								
	145/90	150/95	160/100	170/105	180/110	190/115	200/120	220/130	Control Group
	Number of Patients								
1800-1700	-	2	2	1	-	-	-	-	-
1600-1500	-	-	1	-	1	-	-	-	-
1500-1400	-	5	1	1	1	1	1	-	-
1300-1000	4	10	13	8	2	2	1	-	15
900	-	1	1	1	-	1	-	-	2
800	-	-	1	-	2	-	-	-	-
700	-	-	1	2	2	-	-	-	-
600	-	-	1	1	1	-	2	-	-
500-400	-	-	-	1	1	-	-	2	-
1150-200	-	-	-	-	-	-	-	2	-

The data given in table 5 coincide to a certain degree with those of table 1. They show that disturbance of the kidney blood flow and appearance of pathologic changes in the urine arise at various levels of arterial pressure, which confirms the interdependence of these indices and their insufficiently distinct effect on the height of the arterial pressure. However, growth in the frequency of cases with pathologic changes in the urine and diminished kidney blood flow at a very high arterial pressure may serve as evidence of a certain dependence of the course of hypertension upon the rise of ischemia in the kidneys. The rise of renal ischemia aggravates the course of the disease in the majority of cases.

Thus, it must be considered that centrogenic-nervous mechanisms, the disturbance of whose functions results in the rise and fixation of the ypertonic condition, is of preeminent significance in the pathogenesis of hypertension. Against the background of the disturbed neurogenic regulation of the arterial pressure appear paradoxical spastic reactions in the vascular channel of the kidneys, which produces ischemia of the kidneys with pathologic changes in the urine.

Of definite significance is the functional condition of the kidneys in hypertension, depending upon the intra-renal hemodynamics, which will be the subject of our next paper.

Conclusions

1. The blood supply to the kidneys in patients in stage I and in the majority of those in stage II of hypertension is at a normal level and is 21-27% of the per-minute volume of the blood circulation.

2. Diminution of the kidney blood flow first occurs in stage II of hypertension in the period of appearance of albumin and erythrocytes in the urine, which is a clinical manifestation of ischemia of the kidneys.

3. The use of sedatives and vessel-expanding drugs enables one to improve the blood supply to the kidneys all the way to normal, which manifests itself clinically by a diminution and even disappearance of pathologic changes in the urine.

4. A direct dependence between the level of arterial pressure and renal ischemia is lacking.

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